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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/661,740	FERRELL ET AL.	
	Examiner	Art Unit	
	Jon Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12,13 and 22-51* is/are pending in the application.

4a) Of the above claim(s) *13,22-36 and 39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12,37,38 and 40-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/04; 9/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Action is in response to the communication filed on 3/27/2006.

The amendment filed 3/27/2006 is acknowledged and has been entered.

Claims 12, 13 and 22-51 are currently pending in the application and are addressed herein.

Election/Restrictions

Applicant's election with traverse of Group III (claims 12 and 37-51) and of the species: polymorphism at position 1114 in the reply filed on 3/27/2006 is acknowledged.

The traversal is on the ground(s) that Groups I-IV should be rejoined because VEGF-C and VEGF-D share a low level of structural homology and share a common function as VEGFR-3 ligands and because proteins and genes are related "insofar as the protein encodes the gene, and gene therapy involves introducing a gene to achieve in vivo expression of an encoded protein." Applicants also argue that MPEP 803.02 that if members of a Markush Group are sufficiently few in number and or so closely related that a search and examination of the entire claim can be made without serious burden, the Examiner must examine all of the members of the Markush group on the merits (emphasis added). Applicants contend that MPEP 803.04 suggests that examination of 10 sequences is a reasonable number. Applicants further request that Groups I and II be consolidated into one group and that Groups III and IV also be consolidated into a single group because they share a common classification and because the technical differences are lesser for therapy than between protein and gene therapy, and because there would, allegedly, be little burden to examining the claims in fewer groups.

This is not found persuasive because proteins and genes are not related products as they are structurally and functionally distinct. For instance, proteins are comprised of amino acids and can have a plethora of different functions in a cell, while genes are comprised of nucleic acids which encode and express protein. Therefore, methods of using proteins are distinct from methods of using genes, as previously indicated (see page 3 of the 1/23/06 Office Action). Furthermore, protein therapy methods and gene therapy methods have different classifications, which is prima facie evidence of a serious search burden for searching both protein therapy and gene therapy methods together because, among other reasons, the multiple distinct searches would be required to search protein therapy and gene therapy together. For instance, protein therapy would require searching protein sequence databases while gene therapy would require searching nucleic acid databases. With respect to MPEP 803.04, it is acknowledged that up to 10 sequences *may* be searched together; however, there is no requirement that 10 sequences be searched together. Searching more than one sequence would impose a serious search burden on the Office as it would extend the time required to search the sequence databases. Furthermore, the Groups will not be consolidated into two Groups (protein therapy and gene therapy) because a VEGF-C and VEGF-D therapeutic methods are distinct and there is a serious search burden for searching VEGF-C and VEGF-D together. VEGF-C and VEGF-D are structurally distinct, therefore, a different search would be required for each. For example, different sequence searches would be required for VEGF-C and VEGF-D. Therefore, it would be a serious search burden to search for both VEGF-C and VEGF-D and thus the restriction requirement is appropriate.

Applicants also traverse the species election requirement. Applicants assert that the Examiner "continues to misconstrue the invention by stating that claim 39 "is drawn to missense mutations at multiple codons". Applicants traverse because "applicants are not presently claiming the polymorphisms per se in the elected claims". This is not persuasive. It is acknowledged that the claims are not drawn to the polymorphisms themselves. However, the claims certainly encompass the mutations. As such, it should have been stated that the claims "encompasses missense mutations at multiple codons", rather than "is drawn to missense mutations at multiple codons". Furthermore, Applicants have not stated why the species election requirement, as it applies to the methods that encompass the polymorphisms, would be improper.

Applicants also contend that prosecution history of the parent application shows that examination of method claims generic to multiple polymorphisms does not pose a serious search burden. This is not persuasive because each case is examined on its own merits. Furthermore, the lack of a species election requirement in the parent case is not indicative that it the species election requirement is inappropriate in this case. Additionally, Applicants are reminded that the election of a single polymorphism is a species election requirement and, as stated in the 1/23/2006 Office Action (see page 4), "Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all of the limitations of an allowed generic claim as provided by 37 C.F.R. 1.141." As such, should the generic claim become allowable the additional species will be considered as indicated above.

The requirement is still deemed proper and is therefore made FINAL.

Claims 13 and 22-36 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claim 39 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 3/27/2006.

Claims 12, 37-38 and 40-51 are examined herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12, 37, 38, 40-48, 50 and 51 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 12, 37, 38, 40-48, 50 and 51 encompass "VEGF-C gene therapy products". Looking the specification to for guidance, it is noted that the specification states,

> "Moreover, since the therapeutic VEGF-C is to be administered as recombinant VEGF-C or indirectly via somatic gene therapy, it is within the skill in the art to make and use analogs of human VEGF-C (and polynucleotides that encode such analogs) wherein one or more amino acids have been added, deleted, or replaced with other amino acids, especially with conservative replacements, and wherein the VEGFR-3-stimulatory biological activity has been retained. Analogs that retain VEGFR-3-stimulatory VEGF-C biological activity are contemplated as VEGF-C polypeptides for use in the present invention. In a preferred embodiment, analogs having 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12,

> 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 such modifications and that retain VEGFR-3-stimulatory VEGF-C biological activity are contemplated as VEGF-C polypeptides for use in the present invention. Analogs having a deletion of or substitution for the cysteine residue at position 156 of SEQ ID NO: 4 and that retain VEGFR-3 stimulatory activity..."

Therefore, given the broadest reasonable interpretation consistent with the specification (per MPEP 2111), the claims encompass "gene therapy products" that encode VEGF-C analogs, including variants and fragments of SEQ ID NO: 4 (wild-type VEGF-C). Furthermore, since the claims do not indicate that the VEGF-C gene therapy products actually have VEGFR-3 stimulatory activity, the claims encompass analogs or fragments that do not have VEGFR-3 stimulatory activity. As such the instant claims encompass a genus of VEGF-C gene therapy products that includes an enormous number of different species molecules (possibly millions).

Claims 37 and 38 encompass mutant VEGFR-3 alleles that reduce ligand mediated signaling of the VEGFR-3 polypeptide encoded by the allele when compared to the wild type VEGFR-3 allele. As such, the instant claims encompass a genus of VEGFR-3 alleles includes an enormous number of different species molecules considering every possible VEGFR-3 mutant that could be encompassed by the claims.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

With respect to the genus of VEGF-C gene therapy products encompassed by the claims, the specification has only identified SEQ ID NO: 4 and one specific mutation of SEQ ID NO: 4

(a serine substitution of the cysteine at position 156 of SEQ ID NO: 4) which retain VEGFR-3 stimulatory activity. There is no further guidance provided in the specification indicating which other VEGF-C species encompassed by the claims would be functional and which would not. There is no indication of any specific structure-function relationship identifying any particular domains that are critical for the desired function of the VEGF-C gene therapy products encompassed by the claims. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

With respect to the genus of VEGFR-3 alleles encompassed by the claims, the specification has only identified five specific mutant alleles of VEGFR-3 (SEQ ID NO: 1): missense mutations at codons 857, 1041, 1044, 1049 and 1114 of SEQ ID NO: 1, which have reduced ligand-mediated signaling. There is no further guidance provided in the specification indicating which other species encompassed by the claims would also have reduced ligand-mediated signaling and which would not, nor is there sufficient guidance identifying the sequences which can be mutated to create the mutant alleles encompassed by the claims. Accordingly, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at

page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of molecules, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Therefore, only SEQ ID NO: 4 and the mutant having a serine substitution of the cysteine at codon 156 of SEQ ID NO: 4 meet the written description provision of 35 U.S.C. §112, first paragraph for the genus of VEGF-C gene therapy products encompassed by the claims.

Additionally, only missense mutations at codons 857, 1041, 1044, 1049 and 1114 of SEQ ID NO: 1 meet the written description provision of 35 U.S.C. §112, first paragraph for the genus of VEGFR-3 mutants encompassed by the claims.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).)

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12, 37, 38 and 40-51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, is enabling for:

> A method for ameliorating a symptom caused by hereditary lymphedema comprising administering to a patient with hereditary lymphedema a nucleic acid that encodes and expresses SEQ ID NO: 4 or SEQ ID NO: 4 having a serine substituted for the cysteine at position 156, wherein said nucleic acid is administered locally at a site of edema in the patient, and wherein said patient comprises a mutation of a VEGFR-3 allele that is a missense mutation at codon 1114 of SEQ ID NO: 1, thereby ameliorating a symptom caused by hereditary lymphedema in the patient.
>
> [It is noted that the missense mutation of codon 1114 is the only one indicated above because it is the elected species and the other species have not been considered at this point in time]

However, the specification does not reasonably provide enablement for the full scope encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

> *Wands* states on page 1404,
> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The instant claims are drawn to a gene therapy method for treating hereditary lymphedema by administering a VEGF-C gene therapy vector. As such, the claims are drawn, n general, to a gene therapy method.

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims are very broad. For instance, the claims encompass administering a "VEGF-C gene therapy product" to a patient by any route of administration, including systemic administration, intravenous administration (e.g., see claim 50), intramuscular administration (e.g., claim 51), etc. As such, the claims encompass administering the gene therapy product by any route of administration to treat the symptoms of hereditary lymphedema that may be distal to the site of administration. For instance, one of the symptoms of hereditary lymphedema is edema in a limb. The instant claims encompass treating limb edema in a patient with hereditary lymphedema by administering a VEGF-C gene therapy product by oral administration or by administration to a location other than the affected limb.

The claims also encompass administering any of vast number of VEGF-C gene therapy products, as noted above.

The claims also encompass treating hereditary lymphedema caused by any VEGFR-3 mutant that has reduced ligand-mediated signaling, as indicated above.

The unpredictability of the art and the state of the prior art

Regarding the administration of the therapeutic nucleic acid to a part of the body other locally at a site of edema, it is well established in the art that delivery is one of the key problems of gene therapy. For instance, regarding gene therapy in general, **Anderson (Nature 1998; 392(suppl):25-30)** teaches,

> The challenge is to develop gene therapy as an efficient and safe drug delivery system. The goal is more difficult to achieve than many investigators had predicted... The human body has spent many thousands of years learning to protect itself from the onslaught of environmental hazards, including the incorporation of foreign DNA into its genome. (See p. 25, second paragraph). The ultimate goal of gene therapy research is the development of vectors that can be injected, will target specific cells, will result in safe and efficient gene transfer into a high percentage of those cells, will insert themselves into appropriate regions of the genome (or will persist as stable episomes), will be regulated be either by administered agents or by the body's own physiological signals, will be cost effective and will cure disease. (See p. 30, first paragraph).

Crystal (Science 1995; 270:404-410) also indicates some of the problems regarding gene therapy in general. Specifically, regarding the obstacles of human gene transfer, Crystal teaches, "The [gene transfer] vector (should) be specific for its target, not recognized by the immune system..." (See p. 409, column 2 under "The perfect vector").

Anderson and Crystal indicate that direct delivery of the nucleic acid to the desired site of transfection is critical for delivering the nucleic acid to the appropriate cells, which is required for the nucleic acid to express the encoded therapeutic protein.

There are no other specific VEGF-C (SEQ ID NO: 4) mutants found in the art which have been demonstrated to stimulate the VEGFR-3 receptor. Furthermore, other than those disclosed in the instant specification, there are no other specific human VEGFR-3 receptors (SEQ ID NO: 1) mutants that have reduced ligand-mediated signaling found in the art.

It is noted that a post-filing article **(Karkkainen et al. PNAS 98(22):12677-12682; 2001)** was identified which teaches that a mouse model for primary human lymphedema

(Milroy's disease, also known as hereditary lymphedema) was treated with an adenoviral and AAV vectors that express wild-type VEGF-C which resulted in the successful amelioration of lymphedema symptoms (e.g., see abstract; paragraph bridging pages 12679-12680; page 12680; Figure 2, etc.). It is noted that Karkkainnen also specifically teaches that "[T]he half-life of VEGF-C in the blood circulation is short... and local VEGF-C therapy is thus likely to function without systemic effects." As such, Karkkainen establishes that VEGF-C gene therapy can be used to ameliorate symptoms of hereditary lymphedema, when the gene therapy vector is delivered locally at a site of edema.

Working Examples and Guidance in the Specification

The specification has no working examples with respect to gene therapy for hereditary lymphedema.

Quantity of Experimentation

With respect to the genus of VEGF-C gene therapy products encompassed by the claims, it is noted that the genus encompasses an vast number of different VEGF-C analogs and fragments. Considering that the genus could possible encompass millions of different VEGF-C analogs, an enormous amount of additional experimentation would be required to identify the VEGF-C analogs encompassed by the claims which would be functional in the instant claimed method.

With respect to the site of delivery, in view of the teachings of Anderson, Crystal and Karkkainen, an enormous amount of additional trial and error experimentation would be required in order to establish that the gene therapy vector could be delivered to a site other than locally at a site of edema and still have a therapeutic effect.

Level of the skill in the art

The level of the skill in the art is deemed to be high.

Conclusion

Considering the nature of the invention, the breadth of the claims, the unpredictable nature of the invention as recognized in the prior art, the lack of working examples and limited guidance provided, and the high degree of skill required to practice the invention, it is concluded that the specification does not provide an enabling disclosure commensurate in scope with the instant claims. Therefore, additional experimentation is required before one of skill in the art could make and use the claimed invention to its full scope. The amount of additional experimentation required to perform the broadly claimed invention to its full scope is undue.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 12, 42, 44-47 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,040,157 (Hu et al., cited as reference A9 in the 6/12/2004 IDS).

Hu teaches a method for treating for treating Milroy's disease (hereditary lymphedema) by administering a gene therapy product encoding VEGF2 (which is identical to VEGF-C) to a patient having the disease wherein said administration would necessarily result in the induction

of VEGFR-3 signaling in the lymphatic endothelia of the patient, and reduce edema in the patient, including edema of the limb, and reduce accumulation of lymph fluids in the patient, when administered locally at the sites of edema (e.g., see column 36 line 56-67 and columns 39-40).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 12, and 48-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,040,157 (Hu et al., cited as reference A9 in the 6/12/2004 IDS) as applied to claim12 above, and further in view of Joukov et al. (JBC March 20, 1998, cited as reference C43 in the 1/12/2004 IDS).

Hu teaches a method for treating for treating Milroy's disease (hereditary lymphedema) by administering a gene therapy product encoding VEGF2 (which is identical to VEGF-C) to a patient having the disease, as indicated above.

Hu does not teach that the VEGF2/VEGF-C is a mutant VEGF-C that stimulates phosphorylation of wild-type VEGFR-3, or that said mutant is VEGF-CΔC_{156}.

Joukov teaches a mutant VEGF-C that has a serine substitution for the cysteine at position 156 of SEQ ID NO: 4 wherein the mutant is a selective agonist of VEGFR-3 (e.g., see abstract). It is noted that Joukov also teaches the mutant stimulates phosphorylation of wild-type VEGFR-3 (e.g., see Figure 2).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Hu and Joukov and use the mutant VEGF-C which stimulates phosphorylation of wild-type VEGFR-3 (VEGF) with a reasonable expectation of success.

The motivation to combine the references to create claimed invention is provided by Joukov who teaches that the VEGF-C mutant comprising a serine substitution of the cysteine at position 156 is a selective agonist of VEGFR-3, thus indicating that the mutant VEGF-C would be a desirable VEGFR-3 agonist to use because it would activate VEGFR-3 and not VEGFR-2 (like wild-type VEGF-C).

Claims 12, 37, 38, 40 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,040,157 (Hu et al., cited as reference A9 in the 6/12/2004 IDS) as applied to claim 12 above, and further in view of Kimack et al. (American Journal of Human Genetics, 63 (suppl.): A34 (October 1998), abstract 180).

Hu teaches a method for treating for treating Milroy's disease (hereditary lymphedema) by administering a gene therapy product encoding VEGF2 (which is identical to VEGF-C) to a patient having the disease, as indicated above.

Hu does not teach that the patient with hereditary lymphedema has a missense mutation at codon 1114 of VEGFR-3 (SEQ ID NO: 4) which is in a tyrosine kinase domain, wherein said mutation reduce ligand mediated signaling of the VEGFR-3 polypeptide.

Kimack et al. teaches that a missense mutation at codon 1114 of VEGFR-3 (SEQ ID NO: 4), which is in a tyrosine kinase domain, wherein said mutation would necessarily reduce ligand mediated signaling of the VEGFR-3 polypeptide has been identified in a patient with hereditary lymphedema (see abstract).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Hu and Kimack to treat a patient with hereditary lymphedema by administering a nucleic acid that expresses VEGF-C to the a site of edema wherein the patient has a missense mutation at codon 1114 of VEGFR-3 (SEQ ID NO: 4), which is in a tyrosine kinase domain and wherein said mutation would necessarily reduce ligand mediated signaling of the VEGFR-3 polypeptide, with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to combine the references to create claimed invention because Hu teaches that VEGF-C gene therapy can be used to treat hereditary lymphedema, and Kimack has identified a specific mutation that is found in patients with hereditary lymphedema.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Mon-Fri, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

JON ANGELL
PATENT EXAMINER